II. REMARKS

Prior to the amendments made herein, claims 1 to 16 were pending. Claim 4 has been amended to remove the multiple dependency. Claim 7 has been canceled herein without prejudice. Accordingly, after the amendments made herein are entered, claims 1 to 6 and 8 to 16 will be pending.

Applicants' representative wishes to thank the Examiner for interviewing this case on March 14, 2005. The interview was found to be very productive.

A. Regarding the indefiniteness rejection

Claim 7 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants respectfully traverse the rejection.

Applicants have cancelled claim 7 herein without prejudice. Accordingly, Applicants respectfully request that the rejection be withdrawn.

B. Regarding the anticipation rejections

1. Tsai et al.

Claims 1 to 4, 6, 7, and 9 to 15 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Tsai et al. with Garcia de Palazzo et al. to support inherency. More specifically, it is the Action's position that Garcia de Palazzo teaches that mutant EGFR genes are expressed in many cases of lung cancer and, therefore, Tsai inherently anticipates the claimed invention. Applicants respectfully traverse the rejection.

As the Examiner wrote on page 9 of the previous Office Action (mailed March 11, 2004):

> If the Tsai cells comprise no mutant EGFR, **or if present, but AG825 is not selective for it**, amending claims 1, 9, and 13 to require that the TK inhibitor be "relatively" selective" for the particular mutant comprised in the cell/tissue being treated would put the claims in order for allowance. (emphasis added)

In the previous response, Applicants made these amendments of claims 1, 9 and 13, per the Examiner's suggestion. And, because **there is absolutely no evidence whatsoever that AG825 is relatively selective for mutant EGFR**, Applicants respectfully submit that this rejection should be withdrawn and the claims allowed, as the Examiner stated in the previous Action.

As the Action admits, Tsai makes no mention whatsoever of the presence of mutant EGFR genes. The Action makes this inference of inherency from the teachings of de Palazzo. However, there is not the slightest inference that AG825 is relatively selective for a protein encoded by the mutant EGFR gene (over the wild type), as is now required by the claims. **For this aspect, the Office Action has brought absolutely no evidence for inherency.** As such, Tsai cannot anticipate the claimed invention.

"In relying upon the theory of inherency, the examiner **must** provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). M.P.E.P. 2112 IV.

The case cited, *Ex Parte Levy*, is precisely on point here. In *Levy*, the examiner argued that a reference disclosed an end product that was inherently "biaxially oriented." The Board reversed because the examiner did not provide "objective evidence or cogent technical reasoning" to support the conclusion of inherency. The same result is compelled here. Because the Action has not shown that AG825's relative selectivity for the mutant necessarily flows from the teachings of Tsai, Tsai does not anticipate the claimed invention.

Citing *Best* and *Fitzgerald*, the previous Action states that the Patent Office does not have the facilities to test inhibitors and that the burden of showing a novel or unobvious difference is on Applicants. This is an incorrect application of these cases. As stated in the heading of M.P.E.P. 2112 V, this principle applies only "once a reference teaching product appearing to be substantially identical is made the basis of a rejection, **and** the examiner presents evidence or reasoning tending to show inherency." Other wise, the burden does not shift to Applicants.

Here, the reference (Tsai) deals with a different inhibitor, AG825. And it has not been shown that this inhibitor is "substantially identical" to those claimed. Moreover, the Examiner has not presented any evidence or reasoning showing that AG825 is relatively selective for the mutant. Rather, the Action merely states that the Patent Office cannot test for this characteristic. Accordingly, the burden of showing inherency is still with the Examiner. Since this burden has not been met, this rejection must be withdrawn.

Because, under the law, Tsai does not anticipate the claimed invention, Applicants respectfully request that the rejection be withdrawn.

2. Kufe et al. (U.S. Pat. 6,524,832)

Claims 1 to 4, 6, 7, and 9 to 15 are rejected under **35** U.S.C. § 102(b) as allegedly anticipated by Kufe et al. Applicants respectfully traverse the rejection.

As the Examiner wrote on page 9 of the previous Office Action (mailed March 11, 2004):

> If the Kufe cells comprise no mutant EGFR, **or if present, but genistein is not selective for it**, amending claims 1, 9, and 13 to require that the TK inhibitor be "relatively" selective" for the particular mutant comprised in the cell/tissue being treated would put the claims in order for allowance. (emphasis added)

In the previous response, Applicants made these amendments of claims 1, 9 and 13, per the Examiner's suggestion. And, because **there is absolutely no evidence whatsoever that genistein is relatively selective for mutant EGFR**, Applicants respectfully submit that this rejection should be withdrawn and the claims allowed, as the Examiner stated in the previous Action.

As the Action admits, Kufe makes no mention whatsoever of the presence of mutant EGFR genes. The Action makes this inference of inherency from the other teachings. However, there is not the slightest inference that genistein is relatively selective for a protein encoded by the mutant EGFR gene (over the wild type), as is now required by the claims. **For this aspect, the Office Action has brought absolutely no evidence for inherency.** As such, Kufe cannot anticipate the claimed invention.

"In relying upon the theory of inherency, the examiner **must** provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). M.P.E.P. 2112 IV. The case cited, *Ex Parte Levy*, is precisely on point here, as discussed above in connection with the Tsai rejection. The burden of showing inherency is still the Examiner's, as discussed above in connection with the Tsai rejection. Because the Action has not shown that genistein's relative selectivity for the mutant necessarily flows from the teachings of Kufe, Kufe does not anticipate the claimed invention.

Because, under the law, Kufe does not anticipate the claimed invention, Applicants respectfully request that the rejection be withdrawn.

C. Regarding the obviousness rejections

1. Nagane et al. and Han et al. in view of Kondo et al.

Claims 1 to 16 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Nagane et al. and Han et al. in view of Kondo et al. Applicants respectfully traverse the rejection.

As admitted by the Examiner on page 8 of the previous Office Action (mailed March 11, 2004), "the synergistic effect shown with the combination of a relatively specific TK inhibitor and an apoptosis-inducing/increasing agent constitutes a showing of unexpected results." By contrast, the above-cited references, either alone or in combination, do not teach or suggest such synergism. It is precisely for this reason, as conceded by the Office Action, that the invention, as now claimed, is non-obvious.

The Examiner's position is also the position of the law. As stated in M.P.E.P. § 716.02(a): "Evidence of a greater than expected result [to refute an allegation of obviousness] may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989)."

Moreover, numerous agents are known to treat cancer, even specific cancers. It would not be obvious for the skilled artisan to combine a specific two. None of these references teaches combining the two types of agents as claimed. There is absolutely no reason to expect the skilled artisan to choose these two types of agents from the myriad that are known and available. Moreover, the two types, if used together, could perhaps lead to adverse reactions or other undesirable effects.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

2. Nagane et al. and Han et al. in view of Kondo et al. and further in view of Howell et al.

Claims 1 to 16 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Nagane et al. and Han et al. in view of Kondo et al. and further in view of Howell et al. Applicants respectfully traverse the rejection.

As admitted by the Examiner on page 8 of the previous Office Action (mailed March 11, 2004), "the synergistic effect shown with the combination of a relatively specific TK inhibitor and an apoptosis-inducing/increasing agent constitutes a showing of unexpected results." By contrast, the above-cited references, either alone or in combination, do not teach or suggest such synergism. As conceded by the Action, it is precisely for this reason that the invention, as now claimed, is non-obvious.

The Examiner's position is also the position of the law. As stated in M.P.E.P. § 716.02(a): "Evidence of a greater than expected result [to refute an allegation of obviousness] may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989)."

Moreover, numerous agents are known to treat cancer, even specific cancers. It would not be obvious for the skilled artisan to combine a specific two. None of these references teaches combining the two types of agents as claimed. There is absolutely no reason to expect the skilled artisan to choose these two types of agents from the myriad that are known and available. Moreover, the two types, if used together, could perhaps lead to adverse reactions or other undesirable effects.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

3. Kufe et al. in view of Wagner et al. and Han et al.

Claims 1 to 16 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Kufe et al. in view of Wagner et al. and Han et al. Applicants respectfully traverse the rejection.

As admitted by the Examiner on page 8 of the previous Office Action (mailed March 11, 2004), "the synergistic effect shown with the combination of a relatively specific TK inhibitor and an apoptosis-inducing/increasing agent constitutes a showing of unexpected results." By contrast, the above-cited references, either alone or in combination, do not teach or suggest such synergism. Moreover, as discussed above, **Kufe does not teach or suggest using a TK inhibitor that is relatively selective for the mutant,** as is now claimed. Thus, as conceded by the Action, it is precisely for this reason that the invention, as now claimed, is non-obvious.

The Examiner's position is also the position of the law. As stated in M.P.E.P. § 716.02(a): "Evidence of a greater than expected result [to refute an allegation of obviousness] may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989)."

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Finally, Applicants note that on page 9 of the previous Office Action (mailed March 11, 2004), the Examiner stated that **regardless** of what Tsai or Kufe taught, limiting the TK inhibitor to AG1478 would make such claims allowable. Applicants wish to point out that claims 8, 12 and 16 are so limited. Therefore, these claims certainly should be indicated as allowable.

CONCLUSION

All of the issues raised in the Office Action have been addressed and are believed to have been overcome. Accordingly, it is respectfully submitted that all the claims under examination in the subject application are allowable. Therefore Applicants respectfully request a Notice of Allowance to this effect.

Respectfully submitted,

Sol Sheinbein
Registration No. 25,457

Date: April 14, 2005

Encl.
Request for Continued Examination (RCE)
Request for Two-month Extension of Time